RECEIVED
CENTRAL FAX CENTER
JUL 22 2010

REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present response, claims 103, 105-113, 118 and 120-140 are pending. Claims 128-131 and 139-140 are withdrawn as directed to a non-elected invention. Claims 103, 105-113, 118, 120-127 and 132-138 are under examination. Claims 106 and 121 are amended to be grammatically correct. No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Claim Objections

The Examiner has objected to claims 106 and 121 as grammatically incorrect. Applicants have amended claims 106 and 121 to be grammatically correct.

Rejections under 35 U.S.C. § 103(a)

Selkoe, Solomon, Nordstedt and Penney

Claims 103, 108, 109, 112, 113, 118, 123, 124, 127 and 132 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,262,332 ("Selkoe"), Solomon, *Proc Natl Acad Sci* (1996) 93:452-455 ("Solomon"), PCT Publ. No. WO 97/21728 ("Nordstedt"), and U.S. Patent No. 5,773,007 ("Penney"). This rejection is traversed for the reasons discussed below.

The Examiner cites Selkoe for discussing using antibodies to Aβ for *diagnosis* of Alzheimer's disease (Selkoe at abstract; column 2, lines 36-53). Antibodies are produced by conventional immunization of a laboratory animal with either amyloid containing Aβ or a synthetic peptide (Selkoe at columns 17-18). Although Selkoe asserts that some fragments of about 8 or more amino acids from Aβ are capable of producing antibodies (Selkoe at, *e.g.*, abstract; column 2, lines 36-53; column 4, lines 18-24; column 21, lines 18-22), he also reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide containing residues 1-28 of Aβ (Selkoe at column 21, lines 13-18). Such

teaching would have discouraged the use of small synthetic fragments of Aβ for generating antibodies for purposes of diagnosis, and certainly for the purposes of therapy. Thus, if diagnosis by detecting Aβ were one's goal, and one were to have relied on Selkoe's teaching, one would presumably have selected an antibody raised against Aβ deposits rather than to a synthetic peptide, even one that is 28 amino acids in length, which is 20 amino acids longer than 8 amino acids in length.

Selkoe also does not suggest an antibody binding to an epitope within residues 16-23 of Aβ. Selkoe discusses the minimal size of the peptide, but says nothing about the location of the epitope, other than that antibodies against Aβ1-28 resulted in weak β-AP detection. A fair reading of Selkoe's comment that some fragments of about 8 or more residues can be used for generating antibodies is that a fragment of about 8 residues is the minimum size. There is no apparent reason in Selkoe that the artisan would have felt compelled to test the limits of minimum fragment size and risk possible failure in generating an antibody rather than following the protocol of Selkoe who used an Aβ1-28 fragment (which did not work very well). Common sense suggests such possible failure would have appeared to involve an unnecessary risk of more concern than any minor cost saving from synthesizing a slightly shorter peptide, which risk the artisan could have avoided by using a longer fragment. Furthermore, even if the artisan had the fortitude to test the boundaries of feasibility of fragment size, there would have been no reason for him to select Aβ16-23.

The Examiner cites Solomon for describing antibodies that bind to aggregating epitopes of Aβ. Page 6 of the present Office Action. The Examiner acknowledges that Solomon does not explicitly teach administration of antibodies to patients and does not explicitly identify the Aβ16-23 as an immunogenic fragment. Applicants agree that Solomon does not teach or suggest selecting an Aβ fragment consisting of residues Aβ16-23, nor the therapeutic use of antibody proteins, either passively administered or induced by active immunization in the treatment or prevention of a disease associated with amyloid deposits of Aβ in the brain of a patient.

It would not have been obvious to modify Solomon to use active immunization to generate antibodies. Instead, Solomon discusses experiments to assess the effect of antibodies to

Aβ on aggregation and neurotoxicity of Aβ *in vitro*. Solomon concludes by discussing gene therapy as a means to deliver *nucleic acids encoding antibody fragments* (Solomon at page 454, last paragraph).

Solomon's proposed mechanism of inhibition of aggregation is one of simple antibody binding without a role for the antibody effector system (*i.e.*, antibody-dependent cell-mediated cytoxicity (" ADCC") or complement-dependent cell-mediated cytoxicity ("CDCC")). Solomon's proposal to use antibody fragments is consistent with such a mechanism in that the effector or constant region of an antibody is largely or entirely absent in antibody fragments. The reference to antibody fragments in combination with gene delivery may also reflect a concern that antibodies would not otherwise cross the blood brain barrier in sufficient amounts for a therapeutic effect via the aggregation mechanism.

Switching from passive delivery of antibody fragments to active immunization with peptide fragments would not have been obvious because the antibodies generated from active immunization would be intact antibodies with effector regions. The effector regions would not have a role in the simple binding mechanism proposed by Solomon but would be regarded as potentially disadvantageous in inducing inflammation *(see, e.g.*, Hogarth, *Current Opinion in Immunology* 2002, 14:798–802 cited by the IDS filed September 21, 2009 as cite no. 1193; and, US 5,624,821 cited by the IDS filed May 15, 2006 as cite no 718) and reducing passage of antibodies into the brain due to their size.

It would also not have been obvious from Solomon to select Aβ16-23 as a fragment with which to induce antibodies. The antibodies discussed by Solomon are AMY-33 raised against Aβ1-28, and 6F/3D raised against Aβ8-17. Monoclonal antibody 6F/3D, which partially overlaps the fragment of the present claims, had little or no effect in Solomon's assay. AMY-33, which was reported to inhibit aggregation by Solomon, has an epitope occurring outside residues 13-28 of Aβ.[1] The combination of little or no inhibition of aggregation in an antibody whose epitope partially overlaps residues 16-23 and significant inhibition of

[1] The Declaration of Dr. Peter Seubert submitted in Application Nos. 09/724,319 and 10/923,469, and providing data determining the epitope bound by AMY-33, is attached as Exhibit A.

aggregation in an antibody whose epitope lies outside these residues, would have taught way from rather than toward focusing on residues 16-23.

Therefore, the combined disclosures of Selkoe and Solomon neither taught nor suggested the therapeutic use of antibody proteins for the treatment or prevention of a disease associated with amyloid deposits of Aβ in the brain, nor that Aβ16-23 is a therapeutically useful target.

The Examiner cites Nordstedt for disclosing that the sequence "KLVFF," which corresponds to Aβ residues 16-20, is required for the polymerization or aggregation of Aβ protein. The Examiner acknowledges that Nordstedt does not explicitly teach antibodies which bind to Aβ16-20. Page 6 of the present Office Action. Yet the Examiner concludes that Solomon and Nordstedt taken together guide the artisan to select antibodies against Aβ16-23 for the treatment of Alzheimer's, because Solomon reports antibodies against aggregating epitopes should be used and Nordstedt reports that Aβ16-20 constitutes such an aggregating epitope.

In response, Applicants respectfully point out that Nordstedt can not be cited as fully representative of the thinking of those of skill in the art at the effective filing date of the present application. The art as a whole did not point to the 16-20 region of Aβ as being the key region to focus therapeutic treatments. To the contrary, as, WO 95/08999 taught away from the notion that residues 16-20 are an effective anti-aggregating epitope for targeting therapeutics. The '999 application reports that peptides Lys Leu Val Phe Phe (residues 16-20) and Lys Leu Val Phe Phe Ala Glu (residues 16-22) had no effect in a mouse model of Alzheimer's disease generated by co-injection of an aggregating peptide Aβ12-28, whereas certain other peptides had memory enhancing effects. This result would have suggested that Aβ16-20 and Aβ16-22 were ineffective at inhibiting aggregation of Aβ *in vivo*, and taught away from attempting to develop compounds binding to such epitopes to inhibit aggregation.

Other art pointed to regions other than 16-20 of Aβ as having a role in aggregation or otherwise mediating toxicity. For example, the antibody AMY-33 reported by Solomon binds outside residues 13-28 of Aβ, which is outside of Aβ16-20. The 6F/3D by Solomon raised to residues 8-17 of Aβ had only zero or slight effect. Elsewhere Solomon's group has proposed that residues 1-9 in the N-terminal region of Aβ contribute mainly to

solubility (*see* Frenkel, *et al.*, *J Neuroimmunol* (1999) 95(1-2):136-42 at p. 140, col. 2, second paragraph).[2] In contrast, several groups have reported that the determinant role of Aβ aggregation is at the C-terminus (*see,* Soto, *J. Biol. Chem.* (1995) 270(7):3063-3067[3] at p. 3066, second column, second paragraph (citing to 4 references), and Barrow, *J. Mol. Biol.*, (1992) 225(4):1075-1093,[4] Abstract paragraph 3 and p. 1088, second column, second paragraph). Although not all of these references negate Aβ16-20 having a possible role in aggregation, they do teach away from it being the only residues involved in aggregation. Because virtually the entire length of Aβ has been attributed a role in aggregation, the artisan would not have been motivated to select a minimal peptide around residues 16-20 much less the specific 16-23 peptide claimed.

Accordingly, in the aggregate, the combined disclosures of Selkoe, Solomon and Nordstedt, considered with the references of others in the field at the effective filing date of the present application, did not direct the skilled artisan to immunize with a peptide of 8 amino acids in length; did not teach or suggest that intact antibody proteins, either actively induced or passively administered find use in the therapy or prevention of diseases associated with the formation of amyloid plaques in the brain; and did not direct the skilled artisan to select Aβ16-23 in particular as a target epitope.

The Examiner cites Penney for disclosing carrier molecules. Thus, Penney does not add to the teaching of the other references regarding selecting Aβ16-23 as an immunogen.

For at least these reasons, the combined disclosures of Selkoe, Solomon, Nordstedt and Penney did not render the presently claimed invention obvious. The Examiner is respectfully requested to withdraw this rejection.

---

[2] Frenkel, *et al.*, *Neuroimmunol* (1999) 95:136-142 is attached as Exhibit B.
[3] Soto, *J. Biol. Chem.* (1995) 270(7):3063-3067 is attached as Exhibit C.
[4] Barrow, *J. Mol. Biol.* (1992) 225(4):1075-1093 is attached as Exhibit D.

Selkoe, Solomon, Nordstedt and Penney, further in view of Restifo

Claims 105 and 120 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over Selkoe, Solomon, Nordstedt and Penney, further in view of U.S. Patent No. 5,733,548 ("Restifo"). Claim 105 depends from claim 103; claim 120 depends from claim 118. This rejection is traversed for the same reasons discussed above. The combined disclosures of Selkoe, Solomon, Nordstedt and Penney fail to render the claims obvious, and the inclusion of Restifo does not cure the deficiencies of the primary cited references. The Examiner acknowledges on page 8 of the present Office Action that Restifo does not teach residues 16-23 of Aβ. Therefore, claims 105 and 120 are distinguished for at least the same reasons as other claims.

Selkoe, Solomon, Nordstedt and Penney, further in view of Schenk

Claims 106, 107, 110, 111, 121, 122, 125, 126, 133-135, 137 and 138 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over Selkoe, Solomon, Nordstedt and Penney, further in view of WO 00/72876 ("Schenk"). Claims 106, 107, 110 and 111 depend from claim 103; claims 111, 121, 122, 125, 126, 133-135 and 137 depend from claim 118. This rejection is traversed for the same reasons discussed above. The combined disclosures of Selkoe, Solomon, Nordstedt and Penney fail to render the claims obvious, and the inclusion of Schenk does not cure the deficiencies of the primary cited references. Schenk discusses fragments including Aβ1-5, 1-6, 1-7, 1-10, 3-7, 1-3, 1-4, 1-12, 13-28, 17-28, 1-28, 25-35, 35-40 and 35-42, but does not teach or suggest the specific fragment consisting of residues 16-23 of Aβ (*see*, page 27, lines 30-31). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Selkoe, Solomon, Nordstedt and Penney, further in view of Mossman

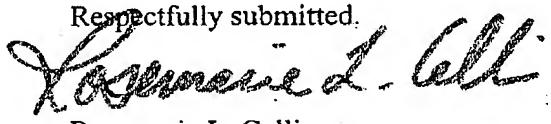
Claim 136 stands rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over Selkoe, Solomon, Nordstedt and Penney, further in view of WO 01/78777 ("Mossman"). Claim 136 depends claim 118. This rejection is traversed for the same reasons discussed above. The combined disclosures of Selkoe, Solomon, Nordstedt and Penney fail to render the claims

obvious, and the inclusion of Mossman does not cure the deficiencies of the primary cited references. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 16-0605.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (650) 838-2000.

Respectfully submitted.



Rosemarie L. Celli
Reg. No. 42,397

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Charlotte Office (704) 444-1000
Fax Charlotte Office (704) 444-1111
Attachments (as noted)
RLC

32027957v1